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Research article

Effect of transcutaneous vagus nerve stimulation with electrical stimulation on generalized anxiety disorder: Study protocol for an assessor-participant blinded, randomized sham-controlled trial

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ABSTRACT

Background: Generalized anxiety disorder (GAD) is the most common type of anxiety disorder and can cause severe damage to patients and increase medical and social burdens. Vagus nerve stimulation (VNS) has been used for treating mental disorders, but the involvement of surgery, perioperative risks, and potentially significant side effects have limited this treatment. Anatomical studies have shown that the ear is the only area where the afferent vagus nerve is distributed on the skin. Recently, the safety and efficacy of transcutaneous auricular vagus nerve stimulation (t-VNS) with electrical stimulation for depression and epilepsy have been objectively evaluated. This trial is trying to evaluate the efficacy of t-VNS with electrical stimulation for the treatment of GAD and explore the potential underlying neural mechanism using fMRI.

Methods: An assessor-participant blinded, randomized sham-controlled trial will be performed. Sixty participants with GAD will be randomly assigned to the t-VNS group or sham t-VNS group. The treatment will last for 8 weeks, once every 30 min and twice a day. Four clinical assessments will be conducted: before treatment, at 2 weeks, at 4 weeks, and posttreatment. The primary outcome parameter is the categorical classification of treatment response in the Hamilton Anxiety Rating Scale (HAMA) score. Functional magnetic resonance imaging (fMRI) scans will be applied, and the alterations in Amplitude of low-frequency fluctuations (ALFF) and functional connectivity (FC) on resting-state fMRI will be compared between the two groups before and after treatment. Moreover, the correlation between the changes in clinical symptoms and the changes in the altered ALFF and FC in the two groups will be analyzed.

Discussion: This high-level evidence-based medical research is expected to evaluate the value of t-VNS in treating GAD and provide a preliminary explanation of its mechanism of action in brain functional imaging. In addition, the use of t-VNS devices has substantially decreased time and financial costs, potentially providing a promising option for complementary alternative medicine in the treatment of GAD, thereby advancing treatment decisions for this condition.

Trial registration: International Traditional Medicine Clinical Trial Registry, ITMCTR2022000099. Registered on June 30, 2022.

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1. Background

Generalized anxiety disorder (GAD) is the most common type of anxiety disorder. This disorder is characterized by excessive anxiety and worry for at least 6 months and is difficult to control [1]. The lifetime prevalence of GAD is 3.7 % [2], and GAD is linked to elevated rates of suicidal tendencies, cardiovascular events, and mortality. Symptoms of GAD include chronic, generalized anxiety and anxiety accompanied by nonspecific physical and psychological symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbance) [3], which lead to severe impairment of the patient's quality of life and social function and increased medical and social burden.

First-line treatments for GAD include psychotherapies such as cognitive behavioral therapy (CBT) and pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [3]. These therapies have been shown to be effective, but 1/3 of the participants had no significant response to treatment. CBT is not suitable for groups of participants with insufficient comprehension, but the clinical use of anti-anxiety and antidepressant drugs may lead to adverse reactions, including dizziness, fatigue, drowsiness, and nausea.

Vagus nerve stimulation (VNS) has been used for treating mental disorders [4,5]. However, the involvement of surgery, perioperative risks, and potentially significant side effects have limited this treatment [6,7]. More recently, the efficacy of transcutaneous auricular vagus nerve stimulation (t-VNS) combined with electrical stimulation for major depressive disorder [8–10], primary insomnia [11], epilepsy [12,13] and mild cognitive impairment [14] has been objectively evaluated. The safety and tolerability of t-VNS are also clear at the doses tested in previous studies [15]. T-VNS has been found to improve symptoms in participants with major depression by regulating the function of the amygdala [16], but there is currently no evidence of the clinical efficacy of t-VNS in the treatment of GAD.

Anatomical studies have shown that the outer ear is innervated by multiple nerves, among which the cymba concha is 100 % innervated by the auricular branch of the vagus nerve [17]. Therefore, the concha is often chosen as the treatment site for t-VNS. Moreover, traditional Chinese medicine (TCM) theory suggests that the five viscera govern emotions and that the concha area also overlaps with the distribution of corresponding visceral areas in TCM ear acupoints. Based on the above theories, we speculate that t-VNS, which stimulates vagus nerve fibers in the ear, should have an effect similar to that of classical VNS in alleviating anxiety symptoms.

This assessor-participant blinded, randomized sham-controlled trial aimed to evaluate the efficacy of t-VNS in the treatment of GAD. The intervention group and the control group used a similar-looking ear clip electroacupuncture device, with the only difference being that the site of action for percutaneous vagus nerve stimulation was different. Moreover, the trial will explore potential neural mechanisms through the use of fMRI.

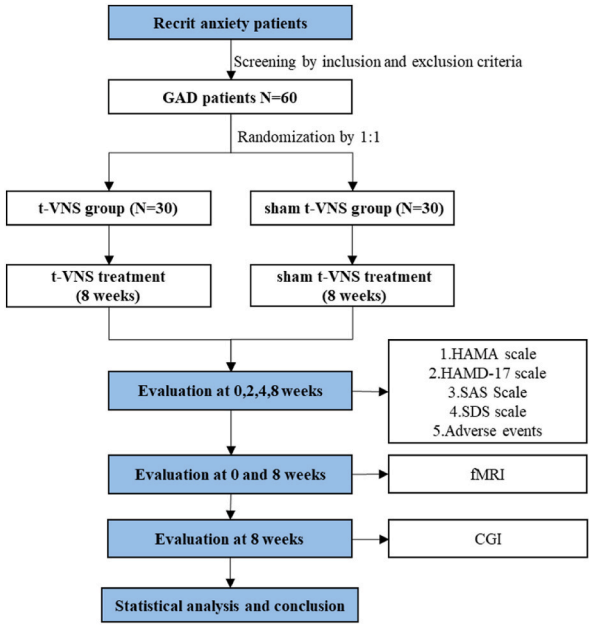

Fig. 1. Flow diagram of the study design. GAD, generalized anxiety disorder; T-VNS, transcutaneous vagus nerve stimulation; HAMA, Hamilton Anxiety Rating Scale; HAMD-17, 17-item Hamilton Depression Scale; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; fMRI, functional magnetic resonance imaging; CGI, Clinical Global Impression.

2. Materials and methods

2.1. Design and setting

The study is a superior, parallel-group, assessor-participant blinded, randomized sham-controlled trial. The recruitment advertisements will be posted at Guang'anmen Hospital, China Academy of Chinese Medical Sciences, and voluntary participation will be ensured for all the volunteers. Sixty eligible participants with GAD were recruited as volunteers and randomly divided into two groups (t-VNS and sham t-VNS), with 30 patients in each group. The t-VNS group comprised the treatment group and received electrical stimulation of the auricular concha region, which has abundant vagus nerves. Sham t-VNS was used for the placebo group, in which patients were subjected to electroacupuncture stimulation of the auricle region with few vagus nerves. The treatment will last eight weeks. Moreover, assessor-participant -blinding is maintained for volunteers and operational implementers. The clinical endpoints will be evaluated by observers who are blinded to the groupings to objectively evaluate the efficacy of t-VNS. We used the SPIRIT reporting guidelines to perform the study [18]. More details of the clinical procedures used are provided in Fig. 1.

2.2. Participants

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is used for the diagnosis of GAD. Participants with mild or moderate GAD will be recruited to participate in the trial. Participants who voluntarily provided signed informed consent and met the inclusion criteria were included in this study. A psychologist will make the diagnosis of GAD.

Participants meeting all the following criteria will be enrolled in the study.

1. The diagnostic criteria for GAD were established according to the DSM-5;
2. Hamilton Anxiety Scale (HAMA) score $\geq$7 and $<$29;
3. Age between 18 and 70 years;
4. Right-handedness;
5. Those who had not used anti-anxiety drugs (including traditional Chinese medicine) or other psychotropic drugs 2 weeks before treatment or who had used but had stopped for 2 weeks;
6. The education level was above junior high school.

Participants meeting any of the following criteria were excluded from the study.

1. Bipolar disorder;
2. Participants with schizophrenia or other mental disorders;
3. Participants with major depressive disorder or severe suicidal tendencies;
4. Participants with serious medical diseases, tumors, or organic lesions of the central nervous system;
5. Alcohol or drug addictions;
6. Those who cannot adhere to treatment due to a long distance or other reasons;
7. Insufficient understanding of this study, unwillingness to participate, poor compliance, refusal to provide informed consent;
8. Contraindications to magnetic resonance scanning;
9. Any lesion on the brain MRI.

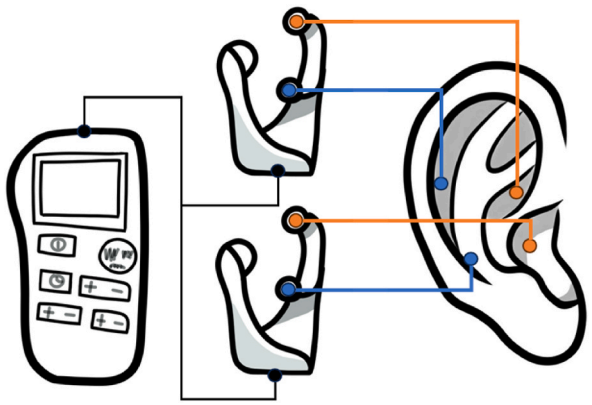

Fig. 2. Functional areas of the t-VNS and sham t-VNS groups. In this figure, the right ear is taken as an example. The orange dot is the region of the concha with abundant branches of the vagus nerves, and the blue dot is the region of the auricle with few vagus nerves. In the t-VNS group, the orange dot represents the main stimulus site, while the blue dot represents the site not stimulated; the opposite is the case in the sham t-VNS group.

If doctors and researchers judge that there is a risk of serious adverse events during the study, the study will be stopped. During the duration of the study, participants will participate voluntarily throughout the study and have the right to withdraw from the trial at any time and for any reason.

2.3. Intervention and comparison

Hua-tuo brand TENS-200A ear vagus nerve stimulators (produced by the Institute of Acupuncture, China Academy of Chinese Medical Sciences, and Suzhou Medical Device Factory) will be used for treatment. The participants will be in a sitting or supine position. Both ears will be treated at the same time. Two ear clips will be placed on each ear with two stimulation points on each clip. After the stimulation points have been disinfected, ear clips will be placed on the ear concha and auricle. The actual treatment points varied depending on the grouping. The electric wire at the stimulation point of the t-VNS is connected to the ear concha, which is full of abundant vagus nerve branches. The electric wire used for stimulating sham t-VNS will be connected to the ear auricle, which contains a few vagus nerves. The specific location is shown in Fig. 2.

The stimulation parameters will include the following: (1) the frequency of the dilatational wave will be 20 Hz, and the wave width will be less than 1 ms; (2) the intensity will be adjusted according to the participant's tolerance ($<$20 mA). Each treatment will last for 30 min, twice a day, for 8 weeks, with a total of 112 times. Participants who will have been treated for more than 80 % of the time (90 times) will be considered per-protocol cases.

The t-VNS device will be self-administered by patients at home. After enrollment, each patient will be individually trained and independently practice using the machine to ensure the accuracy of the treatment; each patient will record on a treatment form, and researchers will inquire intermittently to ensure, as much as possible, the authenticity of the treatment. Each participant will be given a treatment record sheet documenting the duration of the treatment, the intensity of the current, and the response after each treatment to enhance participant adherence during self-treatment.

During treatment, patients are not allowed to take psychiatric drugs.

2.4. Randomization and allocation concealment

Random numbers were generated for 60 subjects using the RAND and RANK functions within Excel software. Participants were divided into a t-VNS group and a sham t-VNS group at a 1:1 ratio, with 30 patients in each group. At the same time, the machine numbering will be completed. The grouping results were coded in order in an opaque and sealed envelope, and the researchers were kept confidential. Patients who meet the experimental requirements will be randomly assigned according to the envelope grouping method. The randomized sequences and envelopes will be stored by relevant teams not involved in other parts of this study.

2.5. Blinding process

As an assessor-participant blinded trial, neither the study investigator nor the participant knows which group the participant is assigned to. The statistician will be blinded for all treatment interventions. To ensure the blinding of both the investigator and the participant, in this study, each participant will have two ear clips per ear, and the stimulator appearance will be exactly the same, with two carbon-impregnated silicon electrodes fixed on each ear clip; however, only one electrode will be connected to an electronic wire embedded in the forceps. Specifically, in the t-VNS group, the upper electrode will be connected to a percutaneous electrical neurostimulator, while in the sham t-VNS group, the lower electrode will be connected to the neurostimulator. After the participants' treatment and completion of all the evaluations, the efficacy of the treatments will be evaluated. If a serious adverse event occurs, the participant's blinding will be removed to determine the relevance of the event to the trial, and further processing and reporting will be conducted.

2.6. Sample size calculations

This study is designed as a randomized controlled trial, with the experimental group receiving t-VNS and the control group receiving sham t-VNS. The primary outcome measure is the categorical classification of treatment response of HAMA, hence the sample size of this study is primarily based on the "efficacy rate", which is defined as the reduction rate of HAMA score $\geq$25 %. Based on the results of 10 preliminary experiments, the efficacy rate p1 in the experimental group is 0.8 (4/5), and the efficacy rate p2 in the control group is 0.4 (2/5). With a two-sided alpha (α) of 0.05 and a power (1-β) of 0.8, the sample size ratio between the experimental and control groups is 1:1. Referring to the method of Chow et al. [19] and using R programming language for calculation, the sample size for the experimental group is determined to be 24 cases, and the same for the control group. Considering a 20 % loss to follow-up and refusal rate, a minimum of 30 cases in the experimental group and 30 in the control group are required, totaling a sample size of 60 cases.

2.7. Clinical data collection and management

The scale evaluation will be conducted by a psychiatrist at the final follow-up, participants' treatment records will be collected to assess adherence and whether they are per-protocol cases. Double data entry and range checks for data values will be implemented to ensure the accuracy of the data.

2.8. MRI data acquisition and preprocessing methods

The fMRI examinations (Siemens Medical, Erlangen, Germany) include T1WI and Blood oxygenation level dependent (BOLD) sequence.

T1WI parameters: time repetition (TR) 2530 ms, echo time (TE) 2.98 ms, slice thickness 1 mm, slice per slab 192, field of view (FOV) 256mm × 256 mm, flip angle (FA) 1°, scan time 6 min 3 s.

BOLD parameters: TR 2000 ms, TE 30 ms, FA 90°, slice thickness 3.5 mm, slice 32, FOV 224 mm × 224 mm, and scan time 6 min 46 s.

Image preprocessing will be performed using the DPARSF 6.0 toolkit of Matlab 2021a platform. The procedure include (1) the DICOM format to NIFTI format, (2) removing the first 10 time points data, (3) slice timing, (4) head movement correction(movement≥2 mm in any direction and 2°were removed), (5) spatial normalization, transforming subjects' functional images into Montreal Neurological Institute (MNI) space, resampling to 3 mm × 3 mm × 3 mm spatial resolution, (6) spatial smoothing using a 6 mm smoothing kernel, (7) linear detrending, (8) regression covariance to remove white matter brain signal, 24 head movement parameters, and cerebrospinal fluid signal, and (9) 0.01–0.08 Hz filtering of the preprocessed images.

2.9. Outcome measures

The primary outcome will be the categorical classification of treatment response in HAMA score, which will be calculated through the following formula: HAMA reduction rate = [(total score before treatment - total score after treatment)/total score before treatment] × 100 %, expressed as a percentage. The criteria for determining clinical efficacy will be as follows: (1) clinical recovery: HAMA <7 points; (2) remakable progress: 75 % > reduction rate of HAMA score ≥50 %; (3) effective: 50 %> reduction rate of HAMA score ≥25 %; and (4) invalid: HAMA subtraction rate <25 %.

The fMRI data will be collected at baseline and at the end of the treatment. The alterations in amplitude of low-frequency fluctuations (ALFF) and functional connectivity (FC)of the resting-state fMRI data will be compared between the two groups before and after treatment. Moreover, the correlation between the changes in clinical symptoms and the altered ALFF and FC in the two groups will be analyzed.

Secondary outcomes will include changes in continuous variable indicators scales of HAMA, Hamilton Depression Scale (HAMD)-17, Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS) scores. These outcomes will be measured at weeks 0, 2, and 4 and at the end of the treatment.

The Clinical Global Impression Index (CGI) will be measured at the end of the treatment.

Safety assessment indicators will be recorded as adverse events (including but not limited to local pain, dizziness, headache, skin lesions, etc.) during treatment. If the participants experience a serious adverse event, the cause of the adverse event will be unblinded and determined.

2.10. Statistical analysis

Statistical analysis will follow the intention-to-treat principle, analyzing the primary efficacy indicators based on the full analysis set. Differences before treatment and 2 weeks, 4 weeks, and 8 weeks after treatment will be used to assess the differences in efficacy between and within groups.

For assessing baseline differences between the two groups, Student's t-test will be used to evaluate normally distributed continuous variables, the non-parametric Mann-Whitney *U* test will be used to evaluate non-normally distributed continuous variables, and the chi-square test or Fisher's exact test will be used to evaluate categorical variables.

Considering the correlations among different repeated measurement data, to control for Type I errors, generalized estimating equations (GEE) will be used to fit the data based on four time points, and examine the within-subject effects according to the measurement occasions [20]. Using the baseline measurements of various scales taken before treatment as covariates, the between-subject effects are tested based on group assignment (0 for the sham t-VNS group, and 1 for the t-VNS group). Additionally, the interaction effect between time and group is examined. In the presence of an interaction effect among the independent variables, simple effects are analyzed, and pairwise comparisons are conducted.

Linear mixed-effects models (LMMs) will be also used for analysis to assess the effect of the intervention over time, with random effects set for patients. LMMs include group prediction (0 for the sham t-VNS group and 1 for the t-VNS group), continuous time (from baseline to eight-week treatment), and intervention-week interaction (group × time) as fixed effects, with the intercept as the only random effect. The coefficient for "group × time" describes the difference in the slope of the outcome trajectory from baseline to eight-week follow-up between the two groups of participants. The "time" coefficient represents the slope of the weekly measurements in the sham control group, while the "group" coefficient represents the difference between the two groups at baseline. With the baseline measurements of various scales before treatment as covariates, the analysis will test for within-subject effects (i.e., main effect of time), between-subject effects (i.e., main effect of group), and the interaction effect of time × group. If there is an interaction effect between the independent variables, simple effects will be analyzed and pairwise comparisons will be made, and type I error will be controlled using the Bonferroni correction [21].

Statistical analysis will be conducted using SPSS 29.0 software. All the statistical tests used will be two-sided. P values less than or equal to 0.05 will be considered to indicate statistically significant differences between the tests.

3. Discussion

The results of this study will clarify the effectiveness of t-VNS combined with electric stimulation in treating GAD and provide strong evidence-based support to overcome the limitations of first-line treatments such as anti-anxiety medications and cognitive behavioral therapy. Furthermore, this study will also provide a preliminary explanation of the mechanism of t-VNS treatment for GAD via brain functional imaging, thereby further understanding the mechanism of auricular holographic theory guided by traditional Chinese medicine theory.

This research design takes into account the subjectivity and instability of generalized anxiety disorder and includes a more ideal control group. By differentiating the experimental group from the placebo control group based on the distribution of the auricular vagus nerve, an assessor-participant blinding design will be employed, in which neither the researchers nor the patients will be aware of the group allocation, to balance the significant impact of the placebo effect on treatment outcomes. The primary outcome measures will focus on the improvement in the subjects' anxiety levels and changes in their brain functional imaging, while the secondary outcome measures will also evaluate the improvement in the patients' depression levels, thus addressing the various mood changes in the patients.

Additionally, the use of t-VNS devices has significantly reduced time and economic costs, potentially offering a new approach for complementary and alternative medicine in the treatment of GAD, thus advancing treatment decisions for GAD.

3.1. Study limitations

The main limitation of this study is that during the blinding process of the participants and researchers, the use of t-VNS equipment may also clamp the concha with abundant branches of the vagus nerves in the sham t-VNS group, which maybe slightly stimulate the vagus nerve. However, the clamp stimulation in sham t-VNS is weaker than the electric stimulation in the VNS group.

CRediT authorship contribution statement

JingLing Lai: Writing – original draft, Data curation. **Jun Liu:** Project administration, Methodology, Data curation. **Lei Zhang:** Data curation. **JiuDong Cao:** Data curation. **Yang Hong:** Data curation. **Ling Zhang:** Formal analysis. **JiLiang Fang:** Methodology. **XiaoLing Wang:** Writing – review & editing, Funding acquisition.

Trial status

This study has been registered on the International Traditional Medicine Clinical Trial Registry (registration number: ITMCTR2022000099, website: http://itmctr.ccebtcm.org.cn/zh-CN). The date of the last refreshed was October 8, 2022. The first participants were included in February 2023. Forty participants will be recruited before this paper is submitted to April 2024. We predict that recruitment will be completed in October 2024.

Abbreviations

CBT	cognitive behavioral therapy
CGI	Clinical Global Impression Index
FC	functional connectivity
fMRI	functional Magnetic Resonance Imaging
GAD	generalized anxiety disorder
HAMA	Hamilton Anxiety Rating Scale
HAMD	Hamilton Depression Scale
SAS	Self-rating Anxiety Scale
SDS	Self-rating Depression Scale
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCM	traditional Chinese medicine
t-VNS	transcutaneous auricular vagus nerve stimulation
VNS	vagus nerve stimulation

Ethics approval and consent to participate

The Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences approved the trial procedure (ethics batch number: 2022-062-KY-01). This protocol was the 4th edition on August 5, 2022. Clinical research will follow the Declaration of Helsinki of the World Medical Assembly and other relevant provisions. The investigator is responsible for informing the subject fully and comprehensively about the purpose, procedure, and possible risks of the study before they are enrolled in this study. The participants will sign a written informed consent form and will be informed that they have the right to withdraw from this study at any time. The informed consent form will be retained as a clinical research document for future reference. During the research process,

the subjects' privacy and data will be protected, and their personal information will not be disclosed.

IPD sharing statement

We will share the original clinical data as needed.

Availability of data and materials

All the original test data and the written informed consent form must be saved and archived and must not be changed without authorization. Researchers and data analysts have access to the final dataset. All adverse events will be recorded in detail, properly handled, and followed up until they are properly resolved or stabilized. Serious adverse events and unexpected events will be promptly reported to the ethics committee and competent authorities in accordance with the regulations, and they will have access to make the final decision to terminate the trial. The principal investigator conducted a cumulative review of all adverse events regularly and convened researchers' meetings to assess the risks and benefits of the study if necessary. The risk of bias in this study will be low, and if adverse events occur, independent data monitoring will be arranged to collect the study data. No additional data are available.

Primary sponsor and secondary sponsor

China Academy of Chinese Medical Sciences and Guang anmen Hospital.

Ancillary and post-trial care and compensation

Patients will receive appropriate ancillary care during the trial. Any adverse events will be assessed, and the necessary support and guidance will be provided.

There were no specific provisions for posttrial care in this study. However, the research team will provide other available treatment options for patients.

If patients suffer harm from the trial, compensation will be provided. The compensation will be determined based on applicable regulations and ethical guidelines. The details of the compensation will be clearly outlined in the informed consent process prior to participant enrollment.

Dissemination policy: trial results

Regardless of whether the results of this study are positive or negative, the findings will be published in peer-reviewed journals and at conferences.

Dissemination policy: authorship

We attempt to ensure that all authors who meet the criteria for authorship are duly recognized for their contributions to this research study.

Dissemination policy: reproducible research

We emphasize the importance of reproducible research and commits to granting public access to the full study protocol.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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